

SPECIFICATION

PROCESSES FOR PREPARATION OF ORGANIC COMPOUNDSTECHNICAL FIELD

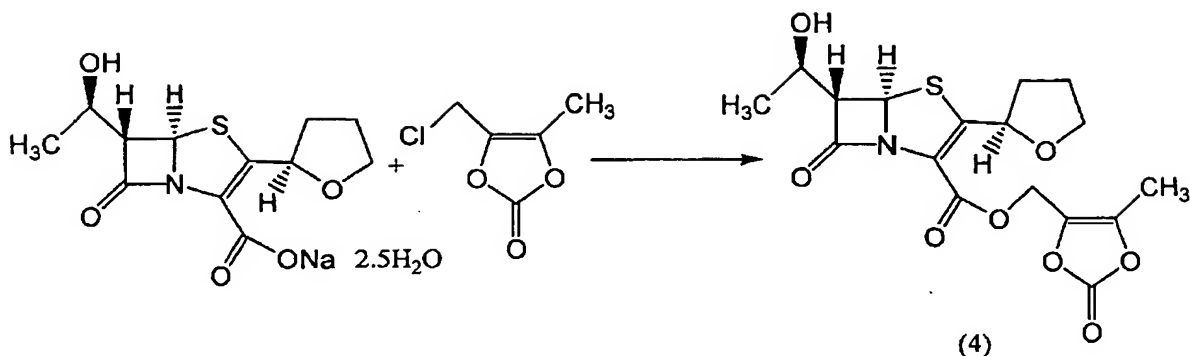
5 The present invention relates to a dehydration method for a polar organic solvent solution containing an unstable organic compound and water.

BACKGROUND ART

10 A compound having a β -lactam ring in its molecule (hereinafter referred to as a " β -lactam compound") is useful as an antibacterial agent with potent antibacterial activity. A wide variety of β -lactam compounds have been developed as antibacterial agents and various β -lactam compounds have been produced on an industrial scale.

15 Although such a β -lactam compound is characterized by having a β -lactam ring in its molecule, this β -lactam ring may be decomposed depending on the type of its substituent, the type of its condensed ring, and/or environmental conditions surrounding its solution (e.g., heat, the
20 presence of water, the property thereof (acidic or alkaline)). For this reason, when β -lactam compounds are to be produced, as mild conditions as possible are selected for their production in order to prevent the compounds from becoming decomposed and causing side reactions during the
25 production process.

 For example, a β -lactam compound (4) useful as an antibacterial agent can be prepared by the reaction shown below.



However, when carrying out the above reaction to
 5 prepare β -lactam compounds on an industrial scale, there is
 a problem arising from a significant reduction in isolated
 yield during the step of isolating the target β -lactam
 compound (4) from the resulting reaction solution.

10 DISCLOSURE OF THE INVENTION

The present invention has been made by taking into
 consideration the above situation, and aims to provide a
 method for preparing an organic compound (e.g., a β -lactam
 compound), which enables efficient isolation of the target
 15 product in high isolated yield.

The inventors of the present invention have made a
 detailed examination of the step where the target β -lactam
 compound (4) is isolated from the reaction solution
 obtained by the above reaction. As a result, the reason
 20 for the reduction in the isolated yield of the β -lactam
 compound (4) would be because in a dehydration step where
 water is distilled off together with THF from a reaction

mixture containing the β -lactam compound (4), distillation reduces the liquid level and hence the highly concentrated solution remaining on the wall surface of the reaction vessel becomes decomposed due to being heated on the vessel wall surface.

In such a dehydration step where water is distilled off together with THF from a reaction solution containing the β -lactam compound (4), the inventors of the present invention have found that when THF and water are distilled off while adding THF to maintain the reaction solution at a constant level, it is possible to avoid the reduction in isolated yield resulting from the decomposition of the β -lactam compound (4). Likewise, in the case of solvent replacement from THF to ethanol (used as a crystallization solvent), they have also found that when THF is distilled off while adding ethanol to maintain the reaction solution at a constant level, it is possible to isolate the target product in high isolated yield. They have made further attempts to adapt such a technique to other cases and have completed the present invention.

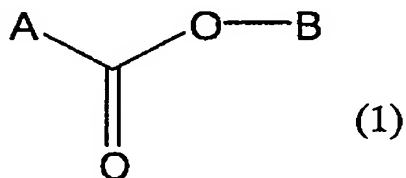
Thus, the present invention provides a method for preparing an organic compound, which comprises a dehydration step of distilling off water from a polar organic solvent solution containing the organic compound and water to bring the concentration of water below a given level, wherein the dehydration step comprises distilling off water together with the polar organic solvent while adding a polar organic solvent to the above polar organic

solvent solution, or comprises repeating several cycles of adding a polar organic solvent to the above polar organic solvent solution and then distilling off water together with the polar organic solvent.

5 In the method of the present invention, the above dehydration step is preferably followed by a crystallization step of distilling off the polar organic solvent from the resulting solution while supplementing the solution with a poor solvent for the organic compound so as
10 to crystallize the organic compound. In this case, an alcohol solvent is preferred for use as a poor solvent.

In the method of the present invention, the organic compound is preferably a β -lactam compound, and more preferably a β -lactam compound of Formula (1):

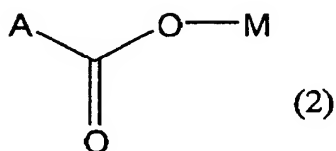
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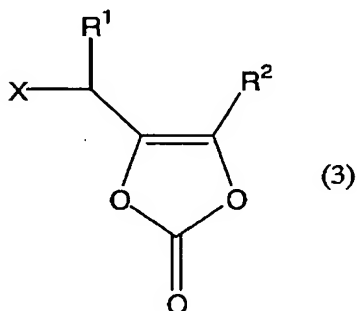
wherein A represents a condensed heterocyclic group having a β -lactam ring structure, and B represents an
20 optionally substituted C_1 - C_{20} alkyl group, an optionally substituted C_2 - C_{20} alkenyl group, an optionally substituted C_2 - C_{20} alkynyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group.

In the method of the present invention, the polar
25 organic solvent solution is preferably a reaction solution

obtained by reacting a compound of Formula (2):



5 wherein A represents a condensed heterocyclic group having a β -lactam ring structure, and M represents a hydrogen atom or a metal atom, in a polar organic solvent, with a 4-halogenomethyldioxolenone compound of Formula (3):



10

 wherein R^1 and R^2 each independently represent a hydrogen atom, an optionally substituted C_1 - C_6 alkyl group or an optionally substituted phenyl group, or R^1 and R^2 may
15 together form an optionally substituted C_3 - C_8 ring, and X represents a halogen atom, or a solution obtained by working up the reaction solution.

MODES FOR CARRYING OUT THE INVENTION

20 The method of the present invention will be further described in more detail below.

1) Polar organic solvent solution

The method of the present invention comprises a dehydration step where a polar organic solvent solution containing an organic compound and water is distilled to
5 remove water together with the polar organic solvent.

(a) Organic compound

Although there is no particular limitation on the organic compound targeted by the method of the present invention, it may be an organic compound which is partially
10 decomposed when exposed to long-term attack by heating in a water-containing organic solvent, especially an organic compound whose decomposition is accelerated depending on the property of water contained in the organic solvent, more specifically under acidic or alkaline conditions.
15 Such an organic compound may be preferred for use in the method of the present invention.

As used herein, the term "decomposition" is intended to mean changing into a compound which is structurally different from the original one. This term encompasses
20 elimination of substituent(s), conversion into a different skeleton, complete breakdown of the skeleton, etc. There is no particular limitation on the degree of decomposition; partial and complete decomposition of the original compound are both intended. In particular, in a case where the
25 method of the present invention is applied to industrial processes, a very slight decrease in yield will affect the purity and product yield of final products. Thus, the method of the present invention is preferably used when

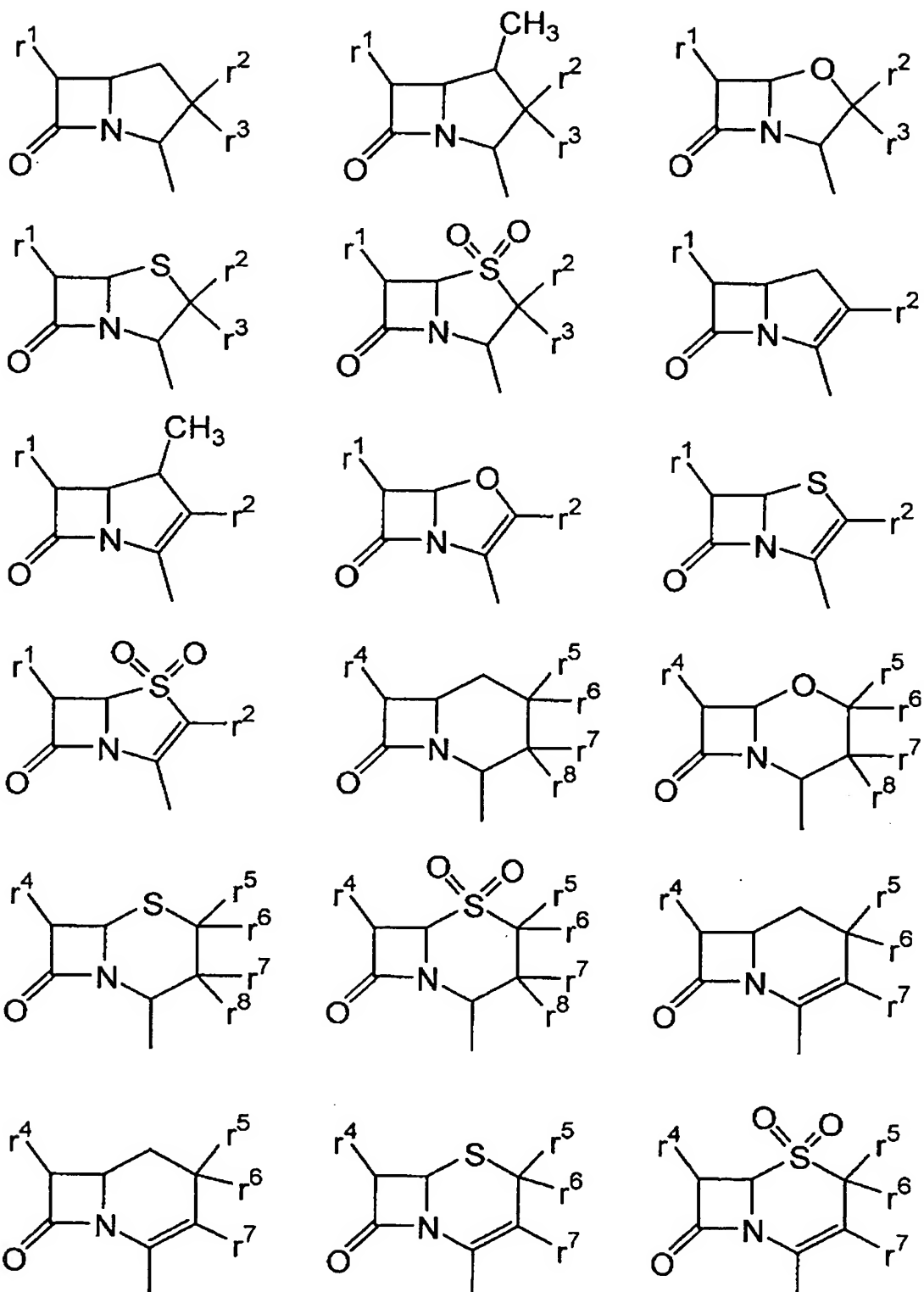
0.1% to several % of the organic compound is decomposed.

Examples of such an organic compound include β -lactam compounds having a β -lactam ring in their molecule; compounds having a hydroxy group protected with a hydrolyzable protecting group such as a tetrahydrofuryloxy group, a tetrahydropyranyloxy group, a t-butoxy group, a 1-ethoxyethoxy group, an acetoxy group, a trimethylsilyloxy group, a triphenylmethoxy group or a 2,2,2-trichloroethoxy group; acetal compounds; hemiacetal compounds; compounds having a C=N bond in their molecule; and compounds having an enolic hydroxy group protected with an acyl group.

Among these compounds, the method of the present invention is preferably used as part of the production process for β -lactam compounds.

β -Lactam compounds are known as active ingredients of β -lactam antibacterial agents. As long as they have a β -lactam ring in their molecule, β -lactam compounds are not limited in any way and include monocyclic compounds and condensed ring compounds. There is also no limitation on the type and number of substituents attached to the β -lactam ring. Among them, preferred are compounds whose molecule carries a condensed heterocyclic group having a β -lactam ring, and particularly preferred are compounds of the above Formula (1).

In the above Formula (1), A represents a condensed heterocyclic group having a β -lactam ring. The following may be mentioned as examples of such a condensed heterocyclic group having a β -lactam ring structure:



In the above formula, r^1 and r^4 each represent a C_1 - C_6 alkyl group which may be substituted with G^1 or a benzoylamino group which may be substituted with G^1 .

r^2 , r^3 , r^5 , r^6 , r^7 and r^8 each independently represent
5 a hydrogen atom, a C_1 - C_6 alkyl group which may be substituted with G^1 , a C_2 - C_6 alkenyl group which may be substituted with G^1 , a C_2 - C_6 alkynyl group which may be substituted with G^1 , an aromatic hydrocarbon group which may be substituted with G^1 or a heterocyclic group which may be substituted with G^1 .

10 In relation to the groups defined for r^1 to r^8 , examples of a C_1 - C_6 alkyl group in the C_1 - C_6 alkyl group which may be substituted with G^1 include a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, a sec-butyl group, a t-butyl group, a n-pentyl group
15 and a n-hexyl group.

Examples of a C_2 - C_6 alkenyl group in the C_2 - C_6 alkenyl group which may be substituted with G^1 include a vinyl group, a n-propenyl group, an isopropenyl group, a butenyl group, a pentenyl group and a hexenyl group.

20 Examples of a C_2 - C_6 alkynyl group in the C_2 - C_6 alkynyl group which may be substituted with G^1 include an ethynyl group, a n-propynyl group, an isopropynyl group, a butynyl group, a pentynyl group and a hexynyl group.

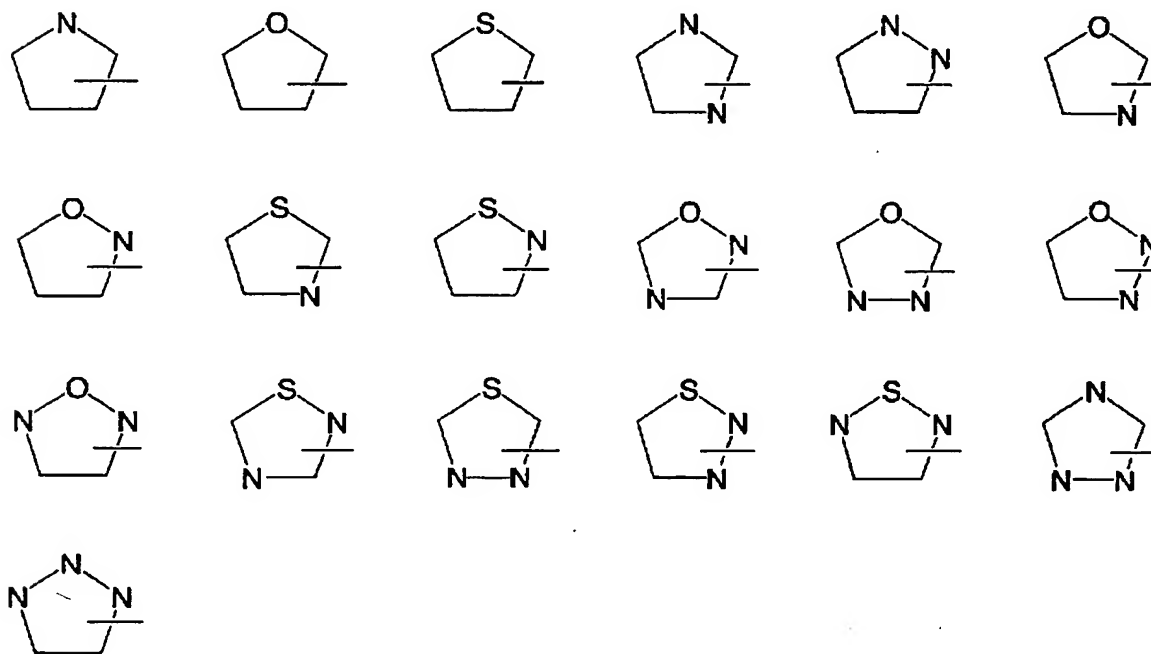
Examples of an aromatic hydrocarbon group in the
25 aromatic hydrocarbon group which may be substituted with G^1 include a phenyl group, a 1-naphthyl group and a 2-naphthyl group.

Likewise, examples of a heterocyclic group in the

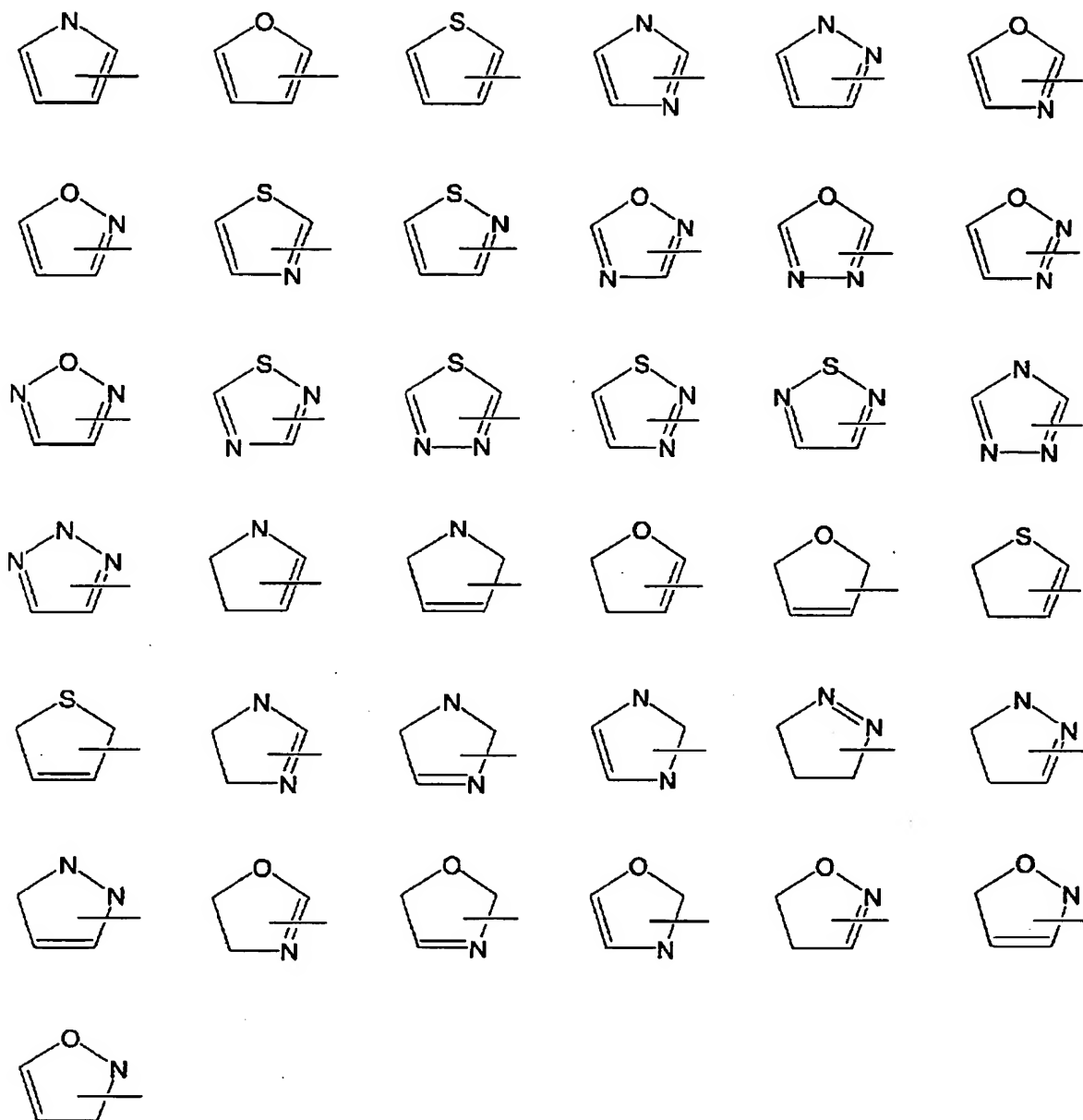
heterocyclic group which may be substituted with G^1 include a 5- or 6-membered saturated or unsaturated heterocyclic group or a condensed heterocyclic group, each of which contains 1 to 4 heteroatoms selected from an oxygen atom, a nitrogen atom and a sulfur atom as ring member(s).

Specific examples include (i) 5-membered saturated heterocyclic groups, (ii) 5-membered unsaturated heterocyclic groups, (iii) 6-membered saturated heterocyclic groups, (iv) 6-membered unsaturated heterocyclic groups and (v) condensed heterocyclic groups, as shown below.

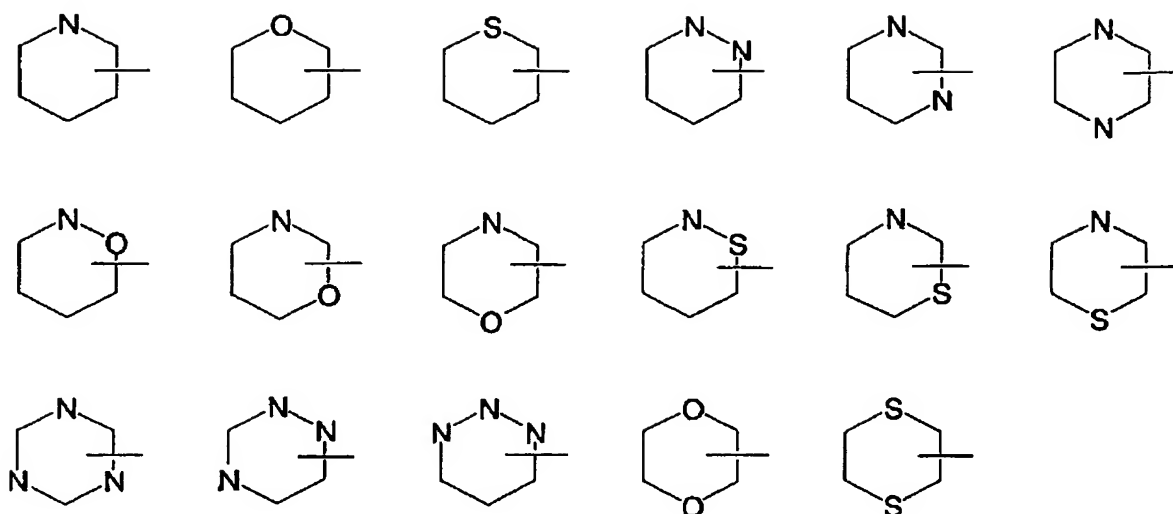
(i) 5-Membered saturated heterocyclic groups



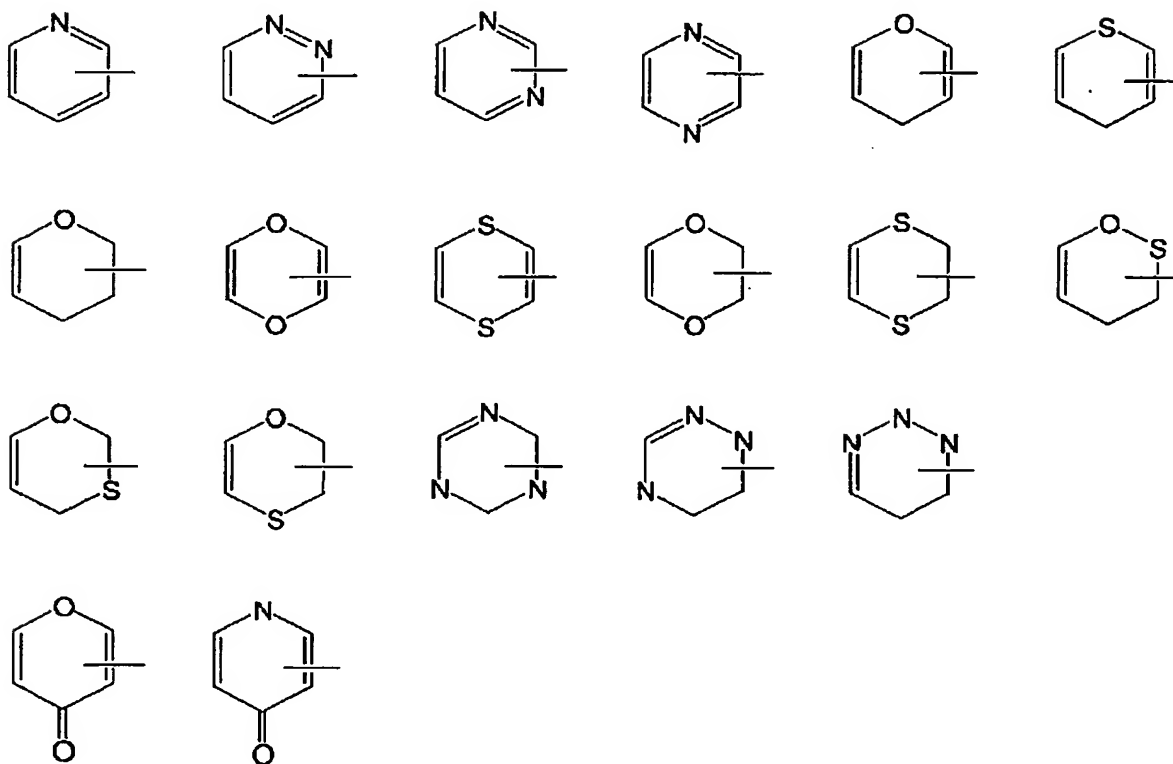
(ii) 5-Membered unsaturated heterocyclic groups



(iii) 6-Membered saturated heterocyclic groups



(iv) 6-Membered unsaturated heterocyclic groups



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(v) Condensed heterocyclic groups

Quinoliny1 groups such as quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl and quinolin-8-yl, as well as isoquinoliny1 groups such as isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl and isoquinolin-8-yl.

Examples of G^1 include a hydroxy group; a nitro group; a cyano group; a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom); a C_1 - C_6 alkoxy group (e.g., a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, a t-butoxy group); a trialkylsilyloxy group (e.g., a trimethylsilyloxy group, a triethylsilyloxy group, a t-butyldimethylsilyloxy group); a C_1 - C_6 alkylthio group (e.g., a methylthio group, an ethylthio group, a n-propylthio group, an isopropylthio group); a C_1 - C_6 alkylsulfinyl group (e.g., a methylsulfinyl group, an ethylsulfinyl group, a n-propylsulfinyl group); a C_1 - C_6 alkylsulfonyl group (e.g., a methylsulfonyl group, an ethylsulfonyl group, a n-propylsulfonyl group, an isopropylsulfonyl group, a n-butylsulfonyl group); an amino group substituted with a C_1 - C_6 alkyl group (e.g., a methylamino group, an ethylamino group, a n-propylamino group, an isopropylamino group); an amino group substituted with two C_1 - C_6 alkyl groups (e.g., a dimethylamino group, a diethylamino group, a methylethylamino group); a C_1 - C_6 alkylcarbonyl group (e.g., an acetyl group, a propionyl group, a propylcarbonyl group); and a C_1 - C_6 alkoxycarbonyl group (e.g., a methoxycarbonyl group, an ethoxycarbonyl

group, a n-propylcarbonyl group, a t-butylcarbonyl group).
The substituent G^1 may be attached at any position.

Alternatively, the same or different substituents G_1 may be attached at several positions.

5 In the above Formula (1), B represents an optionally substituted C_1 - C_{20} alkyl group, an optionally substituted C_2 - C_{20} alkenyl group, an optionally substituted C_2 - C_{20} alkynyl group, an optionally substituted aryl group or an optionally substituted heterocyclic group.

10 Specific examples of the above optionally substituted C_1 - C_{20} alkyl group include:

C_1 - C_{20} alkyl groups, such as a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a t-butyl group, a n-pentyl group, a neopentyl group, a n-hexyl group, an isohexyl group, a n-heptyl group, a n-octyl group, a n-nonyl group and a n-decyl group;

C_1 - C_{20} alkyl groups substituted with oxygen-containing substituent(s), such as a methoxymethyl group, an ethoxymethyl group, a 2-methoxyethyl group, a 3-methoxypropyl group and a 4-methoxybutyl group;

C_1 - C_{20} alkyl groups substituted with sulfur-containing substituent(s), such as a methylthiomethyl group, an ethylthiomethyl group, a 2-methylthioethyl group, a 3-methylthiopropyl group and a 4-methylthiobutyl group;

C_1 - C_{20} alkyl groups substituted with nitrogen-containing substituent(s), such as a dimethylaminomethyl group, a diethylaminomethyl group and a 2-

dimethylaminoethyl group; and

C₁-C₂₀alkyl groups substituted with halogen atom(s), such as a fluoromethyl group, a chloromethyl group, a bromomethyl group, a difluoromethyl group, a dichloromethyl group, a difluoromethyl group, a trifluoromethyl group, a trichloromethyl group, a 2,2,2-trifluoroethyl group, a pentafluoroethyl group, a heptafluoropropyl group, a perfluorobutyl group and a perfluoropentyl group.

Examples of a substituent in the optionally substituted C₂-C₂₀alkenyl group or the optionally substituted C₂-C₂₀alkynyl group include an oxygen-containing substituent, a nitrogen-containing substituent, a sulfur-containing substituent, and a halogen atom. On the other hand, examples of a C₂-C₂₀alkenyl or alkynyl group include the same groups as listed above for G¹.

Examples of the above optionally substituted aryl group include a phenyl group, a 4-methylphenyl group, a 2-chlorophenyl group, a 4-chlorophenyl group, a 3-methoxyphenyl group, a 2,4-dimethylphenyl group, a 1-naphthyl group, a 2-naphthyl group, a 4-chloro-1-naphthyl group and a 6-methyl-2-naphthyl group.

The above optionally substituted heterocyclic group may be either a monocyclic heterocyclic group or a condensed heterocyclic group as long as it is a heterocyclic group containing 1 to 4 nitrogen atoms, oxygen atoms or sulfur atoms as ring member(s). Among them, preferred are a 5-membered heterocyclic ring, a 6-membered heterocyclic ring and a condensed heterocyclic group, each

of which contains 1 to 4 nitrogen atoms, oxygen atoms or sulfur atoms. Specific examples include the same heterocyclic groups as listed above for r^2 , r^3 , r^5 , r^6 , r^7 and r^8 .

5 Examples of a substituent on the heterocyclic group defined for B include a nitro group; a cyano group; a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom); a C_1 - C_6 alkoxy group (e.g., a methoxy group, an ethoxy group, a n-propoxy group, an
10 isopropoxy group, a n-butoxy group, a t-butoxy group); a C_1 - C_6 alkylthio group (e.g., a methylthio group, an ethylthio group, a n-propylthio group, an isopropylthio group, a n-butylthio group, a t-butylthio group); a C_1 - C_6 alkylsulfinyl group (e.g., a methylsulfinyl group, an ethylsulfinyl group,
15 a n-propylsulfinyl group, an isopropylsulfinyl group, a n-butylsulfinyl group, a t-butylsulfinyl group); a C_1 - C_6 alkylsulfonyl group (e.g., a methylsulfonyl group, an ethylsulfonyl group, a n-propylsulfonyl group, an isopropylsulfonyl group, a n-butylsulfonyl group, a
20 t-butylsulfonyl group); an amino group substituted with one C_1 - C_6 alkyl group (e.g., a methylamino group, an ethylamino group, a n-propylamino group); an amino group substituted with two C_1 - C_6 alkyl groups (e.g., a dimethylamino group, a diethylamino group, a dipropylamino group, an
25 ethylmethylamino group, a methylpropylamino group); a C_1 - C_6 alkylcarbonyl group (e.g., an acetyl group, a propionyl group); a C_1 - C_6 alkoxycarbonyl group (e.g., a methoxycarbonyl group, an ethoxycarbonyl group, a n-propoxycarbonyl group,

an isopropoxycarbonyl group, a n-butoxycarbonyl group, a t-butoxycarbonyl group); an optionally substituted phenylsulfinyl group; an optionally substituted phenylsulfonyl group; and an optionally substituted phenylthio group. Two or more of these substituents, which may be the same or different, may be substituted at any position on the heterocyclic ring.

Examples of a substituent on the above phenylsulfinyl group, phenylsulfonyl group or phenylthio group include a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom); a C₁-C₆alkyl group (e.g., a methyl group, an ethyl group); a C₁-C₆haloalkyl group (e.g., a trifluoromethyl group, a 2,2,2-trifluoroethyl group, a pentafluoroethyl group); and a C₁-C₆haloalkoxy group (e.g., a trifluoromethoxy group, a 2,2,2-trifluoroethoxy group, a pentafluoroethoxy group).

(b) Polar organic solvent

The polar organic solvent used in the present invention is not limited in any way as long as it is an organic solvent composed of molecules having a dipole moment. Examples include an ether solvent, a ketone solvent, a halogenated hydrocarbon solvent, a nitrile solvent, an amide solvent, a urea solvent, an ester solvent, a sulfur-containing solvent, and a halogenated aromatic hydrocarbon solvent.

Specific examples include ether solvents such as diethylether, tetrahydrofuran, 1,2-dimethoxyethane and 1,4-dioxane; ketone solvents such as acetone,

methylethylketone, methylisobutylketone and cyclohexanone;
halogenated hydrocarbon solvents such as dichloromethane,
chloroform, carbon tetrachloride and 1,2-dichloroethane;
nitrile solvents such as acetonitrile and benzonitrile;
5 amide solvents such as N,N-dimethylformamide, N,N-
dimethylacetamide, N-methylpyrrolidone and
hexamethylphosphoramide; urea solvents such as
1,3-dimethyl-2-imidazolidinone; ester solvents such as
methyl acetate, ethyl acetate and n-propyl acetate;
10 sulfur-containing solvents such as dimethyl sulfoxide and
sulfolane; as well as halogenated aromatic hydrocarbon
solvents such as chlorobenzene, chlorotoluene,
dichlorotoluene and chloroxylene. The polar organic
solvent solution of the present invention may also comprise
15 two or more of these polar organic solvents.

Among them, preferred is a polar organic solvent that
is available for dissolving both the organic compound and
water and that can be readily distilled off together with
water. Examples of such a polar organic solvent include an
20 ether solvent and a ketone solvent. When using these
solvents, it is preferable to apply the method of the
present invention. Among them, an ether solvent is more
preferred for use and tetrahydrofuran is particularly
preferred for use.

25 (c) Water

Since there is no particular limitation on the amount
(concentration) of water contained in the polar organic
solvent solution used in the present invention, the method

of the present invention can be applied even when using a polar organic solvent solution rich in water (e.g., containing 50% by weight or more of water). Preferably, such a water-rich polar organic solvent solution may be
5 treated using other operations (e.g., partition) to reduce its water content before being provided for the method of the present invention.

(d) Halogen compound

The method of the present invention can preferably be
10 used in a case where the above polar organic solvent solution contains an organic compound, water and a compound which produces, upon coming into contact with water or an alcohol solvent, a substance accelerating the decomposition of the organic compound. A typical example of a substance
15 accelerating the decomposition of the organic compound is a halogen compound.

Examples of such a halogen compound include a halogen (a simple substance; e.g., chlorine, bromine, iodine); a metal halogen compound (e.g., a metal chloride, a metal
20 bromide, a metal iodide); and an organic halogen compound (e.g., an organic chloride, an organic bromide, an organic iodide). Among these halogen compounds, the method of the present invention is particularly effective when the reaction system contains iodine or an alkali metal iodine
25 compound. Examples of an alkali metal iodine compound include lithium iodide, sodium iodide, potassium iodide, magnesium iodide, calcium iodide, ferric iodide, zinc iodide, and cupric iodide.

Although the above polar organic solvent solution is not limited in any way as long as it contains an organic compound and water, it is preferably a reaction solution obtained by reacting a compound of the above Formula (2) with a 4-halogenomethyldioxolenone compound of the above Formula (3) in a polar organic solvent, or a solution obtained by working up the reaction solution (e.g., by washing the reaction solution with water or the like and then collecting the organic layer). In the present invention, the latter solution is preferred because the present invention is preferably intended to ensure a higher yield in isolating a target organic compound.

In the above Formula (2), A is as defined above.

M represents a hydrogen atom; an alkali metal such as lithium, sodium or potassium; an alkaline earth metal such as magnesium or calcium; or a transition metal such as copper(I), copper(II), cobalt(II), cobalt(III), iron (II), iron (III), zinc(II) or manganese(II). In a case where M represents an atom other than hydrogen, a compound of Formula (2) may be in either anhydride or hydrate form.

In the above Formula (3), R₁ and R₂ each independently represent a hydrogen atom, an optionally substituted C₁-C₆alkyl group or an optionally substituted phenyl group.

Examples of a C₁-C₆alkyl group include a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, a sec-butyl group, a t-butyl group, a n-pentyl group and a n-hexyl group.

Examples of a substituent on the above C₁-C₆alkyl

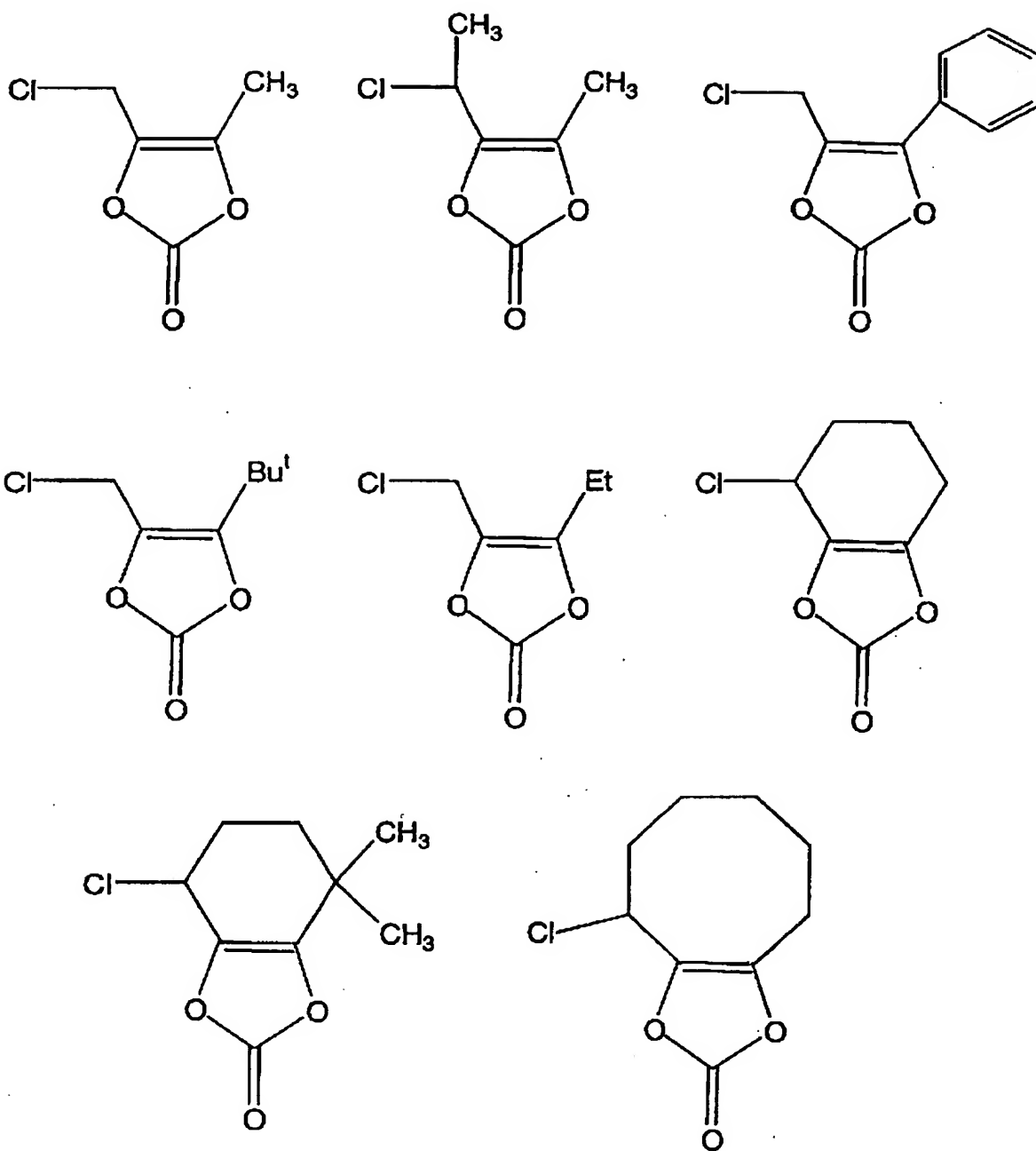
group or phenyl group include a nitro group; a cyano group; a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom, an iodine atom); a C₁-C₆alkoxy group (e.g., a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, a t-butoxy group); a C₁-C₆alkylthio group (e.g., a methylthio group, an ethylthio group, a n-propylthio group, an isopropylthio group, a n-butylthio group, a t-butylthio group); a C₁-C₆alkylsulfinyl group (e.g., a methylsulfinyl group, an ethylsulfinyl group); a C₁-C₆alkylsulfonyl group (e.g., a methylsulfonyl group, an ethylsulfonyl group, a n-propylsulfonyl group, an isopropylsulfonyl group, a n-butylsulfonyl group, a t-butylsulfonyl group); an amino group substituted with one C₁-C₆alkyl group (e.g., a methylamino group, an ethylamino group, a n-propylamino group); an amino group substituted with two C₁-C₆alkyl groups (e.g., a dimethylamino group, a diethylamino group); a C₁-C₆alkylcarbonyl group (e.g., an acetyl group, a propionyl group); a C₁-C₆alkoxycarbonyl group (e.g., a methoxycarbonyl group, an ethoxycarbonyl group); as well as a phenylsulfinyl group which may be substituted with G², a phenylsulfonyl group which may be substituted with G², and a phenylthio group which may be substituted with G².

Examples of G² include a halogen atom (e.g., a fluorine atom, a chlorine atom, a bromine atom); a C₁-C₆alkyl group (e.g., a methyl group, an ethyl group); a C₁-C₆haloalkyl group (e.g., a trifluoromethyl group); and a C₁-C₆haloalkoxy group (e.g., a trifluoromethoxy group).

Alternatively, R_1 and R_2 may together form an optionally substituted C_3 - C_8 ring. Examples of a C_3 - C_8 ring include a cyclopentene ring, a cyclohexene ring, a cycloheptene ring and a cyclooctene ring. Examples of a substituent on the above ring include a C_1 - C_6 alkyl group (e.g., a methyl group, an ethyl group); a C_1 - C_6 alkoxy group (e.g., a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, a n-butoxy group, a t-butoxy group); a halogen atom (e.g., a fluorine atom, a chlorine atom); a C_1 - C_6 alkylthio group (e.g., a methylthio group, an ethylthio group); a substituted amino group (e.g., a dimethylamino group, an acetylamino group); a nitro group; and a cyano group. One or more of these substituents, which may be the same or different, may be substituted at any position.

Among them, preferred as R_1 and R_2 is a hydrogen atom or a C_1 - C_6 alkyl group, and particularly preferred is a hydrogen atom or a methyl group.

The following may be mentioned as specific examples of a preferred 4-halogenomethyldioxolenone compound of the above Formula (3):



A 4-halogenomethyldioxolenone compound of the above
 Formula (3) may be prepared and obtained, for example, by
 5 the method described in USP.4,448,732.

In the reaction between a compound of the above
 Formula (2) and a 4-halogenomethyldioxolenone compound of

the above Formula (3), a phase-transfer catalyst may be added for smooth progress of the reaction. Examples of such a phase-transfer catalyst include quarternary ammonium salts, such as tetraalkylammonium chlorides (e.g.,
5 tetramethylammonium chloride, tetraethylammonium chloride, tetrapropylammonium chloride, tetrabutylammonium chloride (TBAC)); tetraalkylammonium bromides (e.g., tetramethylammonium bromide, tetraethylammonium bromide, tetrapropylammonium bromide, tetrabutylammonium bromide);
10 and benzyltrialkylammonium halides (e.g., benzyltrimethylammonium chloride, benzyltrimethylammonium bromide, benzyl-tri-n-butylammonium chloride (BTBAC), benzyl-tri-n-butylammonium bromide).

In the above reaction, when M in the above Formula
15 (2) represents a hydrogen atom (i.e., the compound of Formula (2) is a carboxylic acid), it is preferable to add a base to the reaction system. Examples of a base available for use include an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide); an alkaline earth
20 metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide); an alkali metal carbonate salt (e.g., sodium carbonate, potassium carbonate); an alkali metal bicarbonate salt (e.g., sodium bicarbonate, potassium bicarbonate); an alkaline earth metal carbonate salt (e.g.,
25 magnesium carbonate, calcium carbonate); a metal hydride (e.g., sodium hydride, calcium hydride); a metal alkoxide (e.g., sodium methoxide, sodium ethoxide, potassium t-butoxide, magnesium methoxide, magnesium ethoxide); and

an organic base (e.g., triethylamine, pyridine).

2) Dehydration step

When the above polar organic solvent solution is distilled to remove water together with the polar organic solvent to obtain an organic compound solution whose concentration of water is below a given level, the present invention is characterized by (a) distilling off water together with the polar organic solvent while continuously adding a polar organic solvent to the above solution, or by (b) repeating several cycles of adding a given amount of a polar organic solvent to the above solution and then distilling off water together with the polar organic solvent from the above solution. It has been found that by using the above procedure (a) or (b), changes in the liquid level in a vessel can be avoided and hence the adhesion of a highly concentrated solution onto the vessel wall surface can be prevented. Consequently, the highly concentrated solution can be prevented from being heated and becoming decomposed on the vessel wall surface.

The polar solvent to be added during the dehydration step may be the same as or different from the polar solvent contained in the above solution. Specific examples include the same polar solvents as listed above for those contained in the above solution.

In the present invention, it is possible to use either of the above procedure (a) or (b). If the position of the liquid interface (horizontal surface) of the solution changes during the dehydration step, the residue

of the solution will be heated more than necessary in a local area with a lowered interface position to increase the risk of producing a compound accelerating the decomposition of the organic compound, thus facilitating the decomposition of the organic compound. For this reason, a heating area of the vessel is preferably kept at substantially the same position as that of the current liquid interface or at a lower position. In order to minimize changes in the liquid interface caused by distillation of the solution, the amount of a polar organic solvent to be added is preferably set to substantially the same amount (volume) as that of the distilled-off polar organic solvent and water.

The dehydration step may be accomplished in a vessel containing the above solution. In a case where the above solution is a reaction solution, the dehydration step may be performed continuously after completion of the reaction in the reaction vessel used for the reaction. Alternatively, a reaction solution may also be transferred to another vessel before being subjected to the dehydration step.

To distill off water together with the polar organic solvent from the above solution, a vessel may be heated to a given temperature. The heating temperature in a vessel will vary also depending on the type of polar organic solvent. A higher heating temperature in a vessel will improve the work efficiency of the dehydration step, but too high a heating temperature can facilitate the

decomposition of the organic compound. Thus, the polar organic solvent and water are preferably distilled off at as low temperature as possible by heating in a vacuum in order to ensure a higher efficiency in distilling off the polar organic solvent and water while preventing the decomposition of the organic compound.

Although the heating temperature for the solution and the degree of vacuum in a vessel during the dehydration step can be determined according to, e.g., the boiling point of the polar organic solvent to be used and the heat stability of the organic compound, it usually ranges from 0°C to 80°C, preferably 10°C to 70°C, and more preferably 20°C to 50°C. The internal pressure of the vessel during heating ranges from 1 to 100 kPa, and preferably 10 to 50 kPa.

Also, the dehydration step is preferably accomplished in a vessel equipped with known distillation equipment. The distillation equipment is not limited in any way as long as it allows collection of the distilled-off polar organic solvent and water. For example, distillation equipment having a piping system, a condenser tube and a collector may be used for this purpose.

In the solution after the dehydration step, water should be removed to the extent that the target organic compound can be obtained in high isolated yield. The water content in the solution after the dehydration step is usually 4% by weight or less, preferably 3.5% by weight or less, based on the total weight of the solution after the

dehydration step. The water content in the solution after the dehydration step can be measured using a known water content meter (e.g., a Karl-Fisher titrator).

3) Crystallization step

5 The organic compound is then isolated from the solution whose water content reaches below a given level.

 Techniques used for isolation of the organic compound include, for example, those involving: (i) distilling off the polar organic solvent from the solution obtained in the dehydration step, and then adding a crystallization solvent to the residue to effect crystallization; (ii) distilling off the polar organic solvent from the solution obtained in the dehydration step while supplementing the solution with a crystallization solvent to crystallize the organic compound; (iii) adding a recrystallization solvent to the residue to effect recrystallization; or (iv) purifying the residue by the technique of column chromatography. As used herein, the term "crystallization solvent" is intended to mean an organic solvent having a low solubility to the organic compound and preferably having a high solubility to impurities, as specifically exemplified by solvents used for recrystallization (recrystallization solvents) and solvents having a considerably low solubility to the organic compound to be crystallized (generally referred to as "poor solvents"). The distinction between poor solvents and recrystallization solvents is not precise; which of them is used depends on the circumstances.

 Among these techniques, (i) or (ii) is preferred for

use and (ii) is particularly preferred. Moreover, techniques (i) and (ii) allow greater reduction in the amount of a crystallization solvent to be used when compared to other techniques.

5 In the above technique (ii), to supplement the solution with a crystallization solvent, a given amount of the crystallization solvent may be added in divided portions or continuously at a constant rate, either of which may be used in the present invention. However, when
10 the volume of the solution is reduced during the crystallization step, the solution is more likely to be concentrated locally at the liquid interface. For this reason, in order to maintain the liquid interface of the solution at a constant position, the amount of a
15 crystallization solvent to be added is preferably set to substantially the same amount (volume) as that of the distilled-off polar organic solvent.

 Although the crystallization solvent to be used is not limited in any way as long as it is a solvent having a
20 low solubility to the organic compound and allowing stable existence of the organic compound without causing its decomposition, an alcohol solvent is preferred for use.

 Examples of an alcohol solvent include C₁-C₆-alcohols such as methanol, ethanol, n-propyl alcohol, isopropyl
25 alcohol, n-butyl alcohol, sec-butyl alcohol, and t-butyl alcohol. Among them, C₁-C₃-alcohols are preferred for use and ethanol is particularly preferred for use.

 The crystallization step may be effected continuously

in the same vessel where the above dehydration step has been performed. Alternatively, the solution obtained in the dehydration step may also be transferred to another vessel where the crystallization step will be performed.

5 The crystallization step may be accomplished by heating a vessel to distill off the polar organic solvent. The heating temperature in a vessel will vary also depending on the type of polar organic solvent. A higher heating temperature will improve the work efficiency of the
10 solvent replacement step, but too high a heating temperature can facilitate the decomposition of the organic compound. Thus, a vessel is preferably heated in a vacuum in order to ensure a higher efficiency in distilling off the polar organic solvent at as low temperature as possible.

15 The solution temperature in the crystallization step usually ranges from 0°C to 80°C, preferably 10°C to 70°C, and more preferably 20°C to 50°C. The internal pressure of the vessel during heating ranges from 1 to 100 kPa, and preferably 5 to 50 kPa.

20 The concentration of the polar organic solvent in the solution after the crystallization step is usually 5% by weight or less, preferably 3% by weight or less, and more preferably 1% by weight or less.

 Once removal of the polar organic solvent has been
25 completed, the resulting solution may be cooled to 10°C or below, preferably 0°C to 10°C, to crystallize the target organic compound. The cooling time required for crystallization usually ranges from several tens of minutes

to several hours.

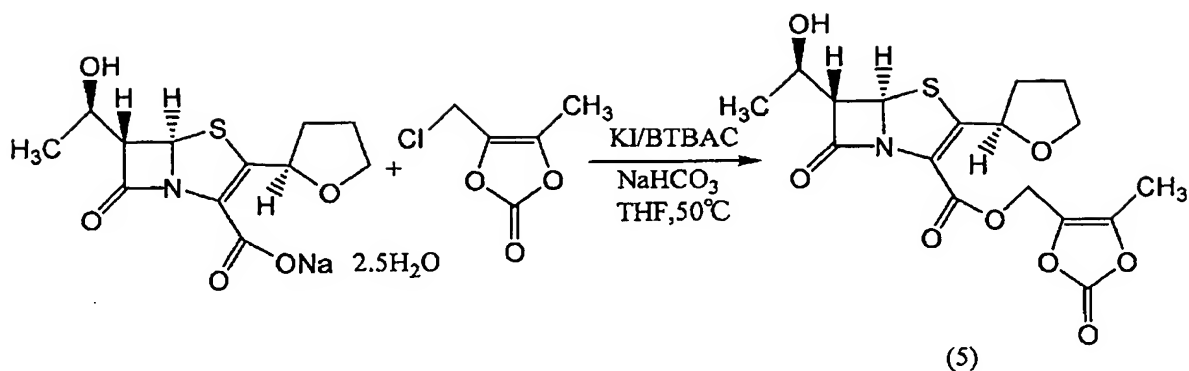
The precipitated organic compound may be isolated, e.g., by filtration or using a centrifugal separator to remove the crystallization solvent. The resulting organic
5 compound may be subject to recrystallization or washed with the same solvent as used for recrystallization or crystallization, if desired.

According to the procedures described above, the target organic compound can be efficiently isolated. The
10 structure of the resulting organic compound may be confirmed by measuring its IR spectrum, mass spectrum and ¹H-NMR spectrum or by gas chromatography, high performance liquid chromatography, etc.

15 EXAMPLES

The present invention will now be further described in more detail in the following examples, which are not intended to limit the scope of the invention.

In the examples and comparative examples shown below,
20 the starting material (5R,6S)-6-(1-(R)-hydroxyethyl)-7-oxo-3-(2-(R)-tetrahydrofuryl)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid sodium salt 2.5-hydrate was prepared according to the method described in JP 63-162694 A.
(Example 1)



(5R,6S)-6-(1-(R)-Hydroxyethyl)-7-oxo-3-(2-(R)-tetrahydrofuryl)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid sodium salt 2.5-hydrate (111.0 g, purity: 98.4%), potassium iodide (5.15 g), sodium bicarbonate (2.60 g) and BTBAC (3.87 g) were mixed in THF (465 ml). To this mixture, 4-chloromethyl-5-methyl-2-oxo-1,3-dioxolene (50.48 g, purity: 97.2%) was added and stirred at 30°C for 2 hours and then at 55°C for 4 hours. After completion of the reaction, the reaction solution was washed once with water (155 ml) and twice with 20% aqueous sodium chloride (155 ml) which had been adjusted to pH 8 with potassium bicarbonate, followed by isolating the organic layer. In this way, a β -lactam compound solution (534.7 g, hereinafter referred to as "Solution A") was obtained, which contained a β -lactam compound of Formula (5) (hereinafter referred to as "Compound (5)"), iodine compounds, water and THF. By quantitative analysis using high performance liquid column chromatography, Solution A was found to contain the target Compound (5) in an amount of 22.44% by weight (yield: 97.4%). The water content in

Solution A was about 4% by weight.

Solution A thus obtained was placed in a vacuum of 17.3 to 19.3 kPa and at a temperature of 20°C to 32°C (bath temperature: 40°C) to distill off THF. Whenever about 90 ml of THF was distilled off, Solution A was supplemented with 90 ml fresh THF. This procedure was repeated three times. In this way, a THF solution of Compound (5) was obtained. The resulting solution was a 0.9 L/mol solution of Compound (5). When the water content in Solution A was measured, it was 0.47% by weight.

Solution A was then warmed to 75°C and THF was distilled off to give a concentrated THF solution of Compound (5) (about 0.25 L/mol in THF), followed by addition of ethanol (95 ml). The resulting solution was stirred to give a homogenous solution and placed in a vacuum of 16 to 20 kPa at 23°C to 40°C (bath temperature: 23°C to 40°C) to distill off THF and ethanol. At this time, ethanol was added dropwise at a constant speed to keep the solution volume unchanged, thus obtaining Solution B. The total amount of ethanol added dropwise was 105 ml. Solution B was a 1.2 L/mol solution of Compound (5).

Solution B was then cooled to 15°C for 30 minutes to crystallize Compound (5). The precipitated crystals were collected by filtration and washed twice with cold ethanol (12 ml). The resulting crystals were dried to give crude crystals of Compound (5) (35.65 g) in 98.9% purity and 88.7% yield.

The crude crystals of Compound (5) were suspended in

ethanol (180 ml) and heated at 60°C for 10 minutes to completely dissolve the crystals. After this solution was filtered under pressure, the resulting filtrate was held at around 30°C for 30 minutes and then placed in a vacuum of
5 10.6 to 13.3 kPa at 30°C to 35°C to distill off 80 ml ethanol. The resulting solution was then cooled at 15°C for 30 minutes to crystallize Compound (5). The crystallized crystals were collected by filtration and washed twice with cold ethanol (13 ml) to give crystals of Compound (5) in
10 99.5% purity and 85.1% yield.

(Example 2)

The same procedure as shown in Example 1 was repeated, except that the step of distilling off THF from Solution A in a vacuum in Example 1 was replaced by the step of
15 distilling off THF while adding dropwise THF through a nozzle reaching near the surface of Solution A. This example produced substantially the same results as Example 1.

(Comparative Example 1)

20 In the step of distilling off THF from Solution A in Example 2, THF was added in one portion (not continuously) prior to distillation. The water content in the solution after distilling off THF was 2% by weight. Subsequently, the same procedure as shown in Example 1 was repeated to
25 isolate Compound (5). Compound (5) was obtained in the same purity as Example 1, but its yield was reduced to as low as 80%.

(Comparative Example 2)

The same procedure as shown in Comparative Example 1 was repeated to isolate Compound (5), except that the step of distilling off THF in Comparative Example 1 was followed by addition of ethanol in one portion (not continuously) to
5 distill off ethanol and THF. Compound (5) was obtained in the same purity as Example 1, but its yield was reduced to as low as 70%. In this case, the mother liquor was found to contain Compound (5) in an amount corresponding to the reduction in yield. When the mother liquor was analyzed
10 for its solvent composition, THF was found to remain in a large amount, which would lead to the reduction in yield because Compound (5) could dissolve in THF. When the amount of ethanol added in one portion was increased 3-fold and the same procedure was repeated, the same results as
15 observed in Comparative Example 1 were obtained for both purity and yield, but the amount of the solvent used was increased.

INDUSTRIAL APPLICABILITY

20 The present invention requires a shorter time for removal of water from a polar organic solvent solution, thus enabling prevention of prolonged heating and hence decomposition of an organic compound in a water-rich polar organic solvent, and also enabling efficient isolation of
25 the organic compound in high isolated yield. Moreover, when the polar organic solvent is distilled off while adding a crystallization solvent, it is possible to reduce the total amount of the crystallization solvent to be used.

This is advantageous in terms of production costs.